RESEARCH ARTICLE

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The Role of Single Voxel MR Spectroscopy, T2 Relaxation Time and Apparent Diffusion Coefficient in Determining the Cellularity of Brain Tumors by MATLAB Software

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Abstract

Introduction: Brain tumors if timely diagnosed are sure to be treated through shorter processes. MRI amongst others is of Para clinical methods greatly effective in diagnosis phase. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps provide some information that could reflect tissue cellularity. Neurosurgeons, in particular to detect the tumor cellularity, must send the specimens taken through biopsy to the pathology unit. This study is aimed at determining the tumor cellularity in brain. **Materials and Methods:** In this cross-sectional study, 32 patients (18 males and 14 females of the range 18 – 77 y/o) between April 2014 and February 2016 who were referred to the neurosurgery department of Shohada-E Tajrish Hospital of Tehran participated. Imaging was made using single voxel MR Spectroscopy, ADC and T2W Multi Echo Pulse Sequence in addition to routine pulse sequences and the images were analyzed using MATLAB software to determine the cellularity of brain tumors in comparison to the biopsy. **Results:** findings showed that by decreasing T2 relaxation time, the amount of ADC, N-Acetyl Aspartate (NAA) and also, increase Choline metabolite, lead to registering tumors in the lower class on the designed table and these tumors have a higher degree of consistency and cellularity. T2 Relaxation time, the tumors will stand at higher class on the designed table. Also the results indicated that 85% diagnostic weight of T2 relaxation time and 83% diagnostic weight of ADC compared with biopsy could reveal the brain tumor cellularity (P>0.05). **Conclusion:** some cellular metabolite changes such as NAA and Choline, ADC value and T2 relaxation time feature could effectively be used to distinguish and illustrate the degree of cellularity of brain tumors especially Intra-axial brain tumors (with about 85%. vs. biopsy). We recommend to more data should be used to increase the accuracy percentage of this technique.

Keywords: MATLAB software- T2 relaxation time- Brain tumor- MRI- MRS

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Introduction

Magnetic resonance spectroscopy (MRS) is a relatively fast, non-invasive method that provides metabolic biochemical information of the normal brain parenchyma and of pathological processes (Ishimaru et al., 2001). It is one of the methods for determining the molecular structures which provides metabolic information from viable brain tissues (Bulakbasi et al., 2003). Metabolites which were extracted and then calculated according them density in the brain tissue include choline (Cho), N-acetyl aspartate (NAA), Creatine (Cr), lactate, Mioinositol (MI), glutamine/glutamate, lipids and etc. Brain lesions contain abnormal quantities of these metabolites compared with normal brain tissue (Ott et al., 1993; Majós et al., 2004). Diffusion-weighted imaging (DWI) and Apparent Diffusion Coefficient (ADC) maps provide some information related to tissue cellularity and integrity (Kono et al., 2001; Yamasaki et al., 2005). Tumors, the masses of cells capable of replication uncontrollably (Madden et al., 2004), could break out in different body tissues and organs. They can be categorized into two general categories of benign and malignant (Doll and Peto, 1981; Little, 2001). In case the brain tumor is rooted in brain Parenchyma, it is referred to as Intra-axial. If it is originated from outside of the brain (or has been developed by Metastasis), it is designated as Extra-axial (Barak, 2006; Pärtan et al., 2003). Although the skull completely covers the brain, it

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is still possible to make a timely diagnosis if only Para clinical equipment and appropriate diagnostic tools are available to determine the brain status (Blank, 2013; Di Luca et al., 2011). Nevertheless the diagnosis most often is prescribed only in cases where unexplainable symptoms appear in patients (Beckles et al., 2003; Hanfling, 1960; Janda et al., 2006). A number of factors like the type, size, origin, cellularity and specially its development process involve in determining the threats emanating from the tumor. (Weinberg, 2013; Schirrmacher, 1985). Moreover, the surgery plan design plays a major role in the spread and intensity of post-surgery side effects (Romano et al., 2009). Accordingly, in case the surgeon can access more comprehensive data about characteristics of the tumor through Para-clinical methods (especially MRI), it would be possible for the neurosurgeons to make necessary changes in the surgery plan so as to minimize the side effects of the operation (Barone et al., 2014). There are some mysteries and unknown aspects in MRI however, such as regarding the extent of cellularity of the tumor to be removed. Conventionally in an invasive method for detect the tumor cellularity, the specimens collected through biopsy are sent to the pathology unit, where the cellularity grading is detected almost precisely. (Cha, 2006; Hayashida et al., 2006; Feiden et al., 1991). The main aim of the present study however, was to reveal some important information on the tumor cellularity through using specific MRI protocols before the surgery without any aggressive procedure and clinical side effect for patient.

Materials and Methods

In this study, all of indicated patient who suffered from brain tumors include 32 patients (18 males and 14 females of the range 18 – 77 y/o) who were referred to the neurosurgery department of Shohada-E Tajrish Hospital of Tehran between April 2012 and February 2014 were randomly selected to participate in this research. It was used Siemens Avanto MRI 1.5 T equipment together with special holding pads to perform MRI pulse sequences on the quadrature brain coil. Initial analysis of the images was conducted with MRI Syngo B17 software (Weale, 2011) and afterwards, the final analysis was done using MATLAB software. The following program was written in MATLAB analysis program to extract ADC value and T2 relaxation time (in appendix file).

Initially the MRI exam was carried out on the samples comprising of routine sequence as well as the intended sequence of the study that was SVS-MRS (STEAM), T2-SE Multi echoes (16 echoes) and DWI-EPI with b value 0 and 1,000 s/mm^2 (Table 1). The images were primarily processed using MRI scanner (Figures 2 to 4) and final processing of the images was conducted using MATLAB software. The outputs were then recorded next to the tumor cellularity identified by the surgeon during the surgery. The patients were positioned head first and supine. After setting up of the quadrature coil for taking images of the brain meanwhile holding pads, the patient was sent into the magnet for scanning. Using the optimized parameters depicted in Table (1). first the brain routine pulse sequences including FLAIR, T1W, T2W in axial plane and T2W in coronal plane, as well as the T1W in sagittal plane and finally the T2W Multi echo pulse sequence and DWI in axial plane (Figure 1 and 2) were prepared.

To reduce time, the Parallel Imaging technique, Generalized Auto calibrating Partially Parallel Acquisition (GRAPPA) with Acceleration factor of 2 was used in all sequences. The data obtained from MRI and the tumor cellularity results were stored into three individual files to be retrieved by MATLAB software for final analysis. The files 1 to 3 relate to the information on the patients with tumor cellularity degree between1 to 3. For each file the relevant table represents the mean of signal intensity per echo which ranges from 22 to 352 milliseconds with echo intervals of 22 milliseconds. The cellularity of tumor determined by the surgeon during surgery was divided into three classes:

1- Tumors that cannot be suction and should be cut using razor sharp tools.

2- Tumors that can be crushed and suction.

3- Tumors that can be suction, but are not liquid or necrotic structure.

MATLAB software program consists of four functions which include Main, Feature, Train and Weight. The Functions take the features and vectors from the file of images and extract the features. The features include T2 relaxation time, the slope of graph T2 relaxation time, and the maximum slope of graph T2 relaxation time.

Results

The extracted feature of MATLAB software in this

Table 1. Parameters of Routine Brain Pulse Sequence That were Performed in This Study

parameters	Plane	TR (ms)	TE (ms)	Matrix size	FOV (cm)	Slice thickness (mm)	ETL
Sequences	Axial	3700	113	320×256	26	5	17
T2W-FSE	Axial	410	9	320×256	24	5	2
T1W-FSE	Axial	8000	90	320×256	24	5	11
FLAIR	Coronal	3700	113	320×256	23	4	17
T2W-FSE	Sagittal	410	9	320×256	24	4	2
T2W SE-Multi echo	Axial	3000	22 - 44- …352	320×256	24	4	-
DWI	Axial	3100	91	128×128	26	5	-
SVS-MRS	-	3500	270	1×1×1	1	10	-

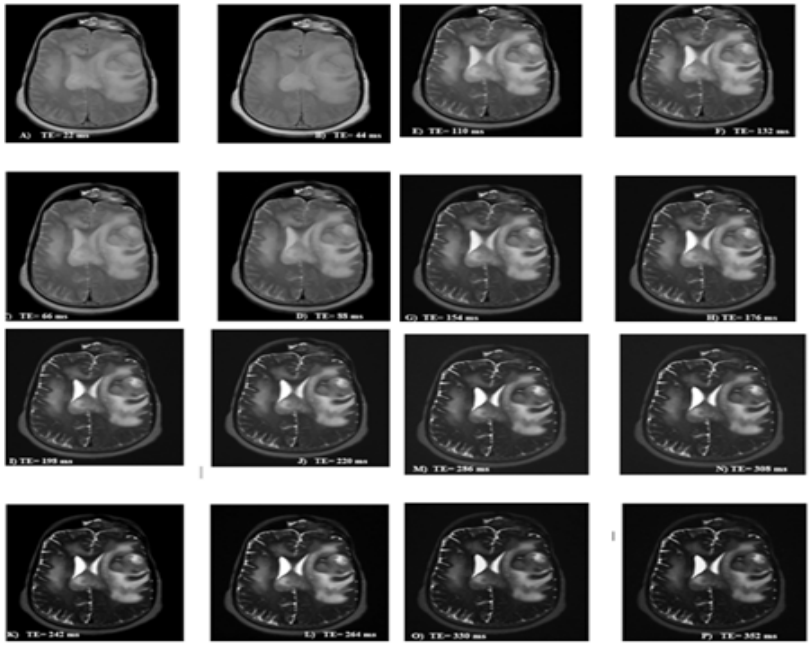

Figure 1. Images Provided in Sequence (T2 SE Multi echo echo-16) from a Patient who Suffers from Tumor GBM by TR Equal to 3000 ms and a TE of 22 ms (Figure A) to 352 ms (Figure P). Interval between the echoes is 22 ms, respectively, of the image A to P. By increasing echo time, T2 contrast of the image may be biased heavy.

study indicated that the best feature compared with the biopsy method to show the extent of cellularity among other features mentioned above was 'T2 relaxation time'. Another effective extracted feature was ADC with 82.7% and then, the slope of T2 relaxation time with 81% diagnostic accuracy compared to gold standard which is biopsy. Finally, the maximum slope of T2 relaxation curve feature indicated 79% diagnostic accuracy compare to biopsy. As was mentioned earlier, the more the weight of a feature, the higher capability it possesses to distinguish between the classes of a tumor cellularity. Also, as more as decrease NAA/ Cho in MRS indicate the high grade of tumor malignancy and cellularity (Figure 5).

As is provided in ROI (Figure 2) and signal intensity in ROI (Figure 3). the T2 relaxation time has a direct relationship with the structures and inter-molecular bond type of each substance and tissue. ADC also indicate the degree of water molecule diffusedly in the intercellular

Table 2. Diagram T2 Relaxation Time Related to Drawing ROI by MRI Scanner That Horizontal Axis is TE and the Vertical Axis is Signal Intensity. As can be Observed, with Increasing TE, the Signal Intensity Decreases

Echo time	ROI 1			ROI 2			ROI 3		
	Mean	S.dev	Area	Mean	S.dev	Area	Mean	S.dev	Area
22	823.9	25.9	0.1	790.4	6.2	0.1	8.11.2	6.6	0.1
44	734.6	19.1	0.1	739.1	4.6	0.1	739.3	6.8	0.1
66	585.8	17.8	0.1	607.6	5.7	0.1	581.5	11	0.1
88	526.3	18.4	0.1	540.6	7.7	0.1	517.6	8.5	0.1
110	428.3	19.4	0.1	461.8	13.4	0.1	420	9.3	0.1
132	377.1	13.5	0.1	412.7	7.1	0.1	372.8	4.4	0.1
154	311.7	19.1	0.1	353.2	7.5	0.1	302	6.1	0.1
176	275.5	18.8	0.1	315.3	7.8	0.1	270.3	6	0.1
198	228.5	19.2	0.1	267.3	6.4	0.1	227.5	3.4	0.1
220	203.1	14	0.1	243	6.1	0.1	201.2	3.9	0.1
242	171.4	10.6	0.1	207.5	8.4	0.1	165.5	5.6	0.1
264	147.4	11.7	0.1	187	8.1	0.1	146.4	5.7	0.1
286	124.1	10.5	0.1	165.3	8.3	0.1	124.8	5.9	0.1
308	110	10.6	0.1	141.8	5.5	0.1	111.8	4.8	0.1
330	95.5	10.7	0.1	132.1	9	0.1	98.4	4.1	0.1
352	86.8	8.9	0.1	110.6	7.6	0.1	85.8	3.7	0.1

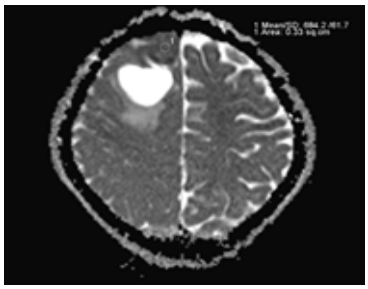

Figure 2. ADC Map of the Oligo Astrocytoma Tumor in a Patient with Cystic Mass that has Cellularity of Grade 3. This image is at the initial analysis; three ROI is drawn on the solid part of tumor.

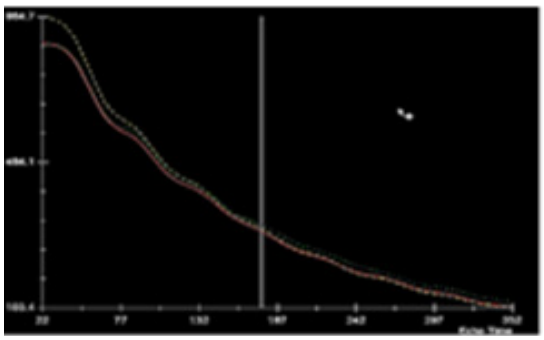

Figure 3. Diagram T2 Relaxation Time Related to Drawing ROI by MRI Scanner That Horizontal Axis is TE and the Vertical Axis is Signal Intensity. As can be observed, with increasing TE, the signal intensity decreases

Echo Time	ROI 1			ROI 2			ROI 3			ROI 4		
	Mean	SDev	Area	Mean	SDev	Area	Mean	SDev	Area	Mean	SDev	Area
22	823.9	25.9	0.1	790.4	6.2	0.1	811.2	6.6	0.1			
44	743.6	19.1	0.1	739.1	4.6	0.1	739.3	6.8	0.1			
66	585.8	17.8	0.1	607.6	5.7	0.1	581.5	11.0	0.1			
88	526.3	18.4	0.1	540.6	7.7	0.1	517.6	8.5	0.1			
110	428.3	19.4	0.1	461.8	13.4	0.1	420.0	9.3	0.1			
132	377.1	13.5	0.1	412.7	7.1	0.1	372.8	4.4	0.1			
154	311.7	19.1	0.1	352.5	7.5	0.1	302.0	6.1	0.1			
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198	228.5	19.2	0.1	267.3	6.4	0.1	227.5	3.4	0.1			
220	203.1	14.0	0.1	243.0	6.1	0.1	201.2	3.9	0.1			
242	171.4	10.6	0.1	207.5	8.4	0.1	165.5	5.6	0.1			
264	147.4	11.7	0.1	187.0	8.1	0.1	146.4	5.7	0.1			
286	124.1	10.5	0.1	165.3	8.3	0.1	124.8	5.9	0.1			
308	110.0	10.6	0.1	141.8	5.5	0.1	111.8	4.8	0.1			
330	95.5	10.7	0.1	132.1	9.0	0.1	98.4	4.1	0.1			
352	86.8	8.9	0.1	110.6	7.6	0.1	85.8	3.7	0.1			

Figure 4. Diagram of Tables of Numerical Values in Figure 3-4, Each Column Corresponding to Each ROI Values and Standard Deviations of the Mean of Signal Intensity of Each Echo Has been Write

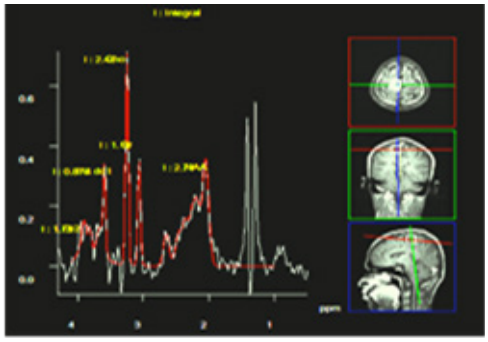

Figure 5. The Spectrum of SVS-MRS in the Patient with Malignant Brain Tumor Show that the NAA Decreased and the Choline Was Increased

tissue, it is evident that an increase in the tissue intensity as well as in the strength of inter-molecule relations will cause the reduction of T2 relaxation time and ADC of the issue. The reason is that the inter-actions among spins or hydrogen of that tissue are higher and that the tissue gets diffused quicker and appears to be darker on images with T2 weighted contrast and also restrict in water diffusion.

Discussion

The aim of this study was to show the role of MRI in distinguishing the degree of cellularity of brain tumors. For this purpose, some advance MRI techniques such as SVS- MRS, SE multi echo and SE-DWI sequences with helping MATLAB software was used to determine the T2 relaxation time, ADC value of tumor tissues and also cellular metabolite changes in solid tumor tissues in order to identify the relationship between cellularity with ADC value, T2 relaxation time and cellular metabolite changes. The extracted feature using MATLAB software revealed that T2 relaxation time feature had the highest diagnostic accuracy between all features in comparison to the biopsy due to direct relationship with tissue cellularity; it was also capable of specifying the extent of cellularity among the features mentioned above. T2 relaxation time feature extracted from optimized sequences such as SE-Multi echo was capable to register molecular cellularity. Using advanced analysis software can help to achieve beneficial results on a tumor cellularity. It seems that the higher the extent of cellularity of a tissue or lesion is; a steeper slope of curve will be represented in the T2 relaxation time of the tissue or lesion and increase the amount of Choline and also, decrease the NAA metabolite (Gauvain et al., 2001; Norfray et al., 1999). It's worth mentioning that other quantitative and observational studies' results confirm the results of our study (Hayashida et al., 2006; Kono et al., 2001; Coderre et al., 1998). In some similar studies, the tumor cellularity was evaluated based on quantitative study and according to the signal intensity of tumors in PDw and T2w, the diagnostic accuracy result was low (Xu et al., 2007; Castillo et al., 2004). Signal intensity with T2 contrast directly relates to molecule structure of each substance and/or tumoral tissues. Regarding the T2 relaxation time feature, it can be said the higher the cellularity of a tissue or lesion is, the steeper T2 relaxation time curve of the tissue or lesion will be decrease (Abdolmohammadi et al., 2016).

Research limitations: The main drawback of this study was the relatively small number of patients. Although the number of patients was sufficient for a clinical trial, but the design of such functions in MATLAB software requires larger number of samples to effectively pattern the recognition for complete definition and analysis with highest reliability.

The results of this study showed that the features defined for the software indicated that the T2 relaxation time feature was the best to distinguish and to present

the degree of Intra-axial brain tumors cellularity (85%. Accuracy compared to biopsy). It was because this feature with a slight difference, in contrast to other features had the highest weight. In other words, the more the weight of the feature, the higher capability and certainty it possessed in distinguishing the classes of a tumor cellularity.

The findings showed that T2 relaxation time of highly consistent tumors was lower, and the T2 relaxation time curve had a steeper slope with a maximum peak. Moreover, based on the tumor cellularity classification, the tumor falls into a lower class. In contrast, an increase in T2 relaxation time was accompanied by a reduction in tumors cellularity. As more as decrease the NAA/Cho in MRS, indicate the tumor malignancy and cellularity. The most clinical application of this study can be reduction of the number of biopsy of brain tumors to determine the tumor cellularity. This study can be continued in some other areas like pituitary gland and liver lesions. (Provenzaleet al., 2006).

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